IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

ORION CORPORATION, Plaintiff/Counterclaim Defendant, v. WOCKHARDT USA, INC., and WOCKHARDT LIMITED, Defendants/Counterclaim Plaintiffs.	)	C. A. No. 07-550 (GMS)

ANSWER AND COUNTERCLAIMS

Wockhardt USA, Inc. ("Wockhardt USA"), for its Answer and Counterclaims to the Complaint of Orion Corporation ("Orion"), states as follows:

1. Upon information and belief, Wockhardt USA admits that Orion is a Finnish company and has a regular or principal place of business at Orionintie 1, FI-02200 Espoo, Finland. Wockhardt USA lacks knowledge or information sufficient to form a belief as to the truth of the remaining averments of paragraph 1 and, therefore, denies the same.

2. Wockhardt USA admits the averments of paragraph 2.

3. Wockhardt USA admits that Wockhardt USA is a wholly-owned subsidiary of Wockhardt EU Operations (Swiss) AG, which, in turn, is a wholly-owned subsidiary of Wockhardt Limited. Wockhardt USA further admits that Wockhardt USA's website lists an office at 75 Ronald Reagan Boulevard, Warwick, New York, 10990. Further answering, Wockhardt USA states that it has a place of business at 135 Route 202/206, Bedminster, New Jersey, 07921. Wockhardt USA denies the remaining averments of paragraph 3.

4. Wockhardt USA admits that Wockhardt Limited is in the business of researching, developing, manufacturing and marketing generic pharmaceutical products. Wockhardt USA admits that Wockhardt USA markets in the United States certain generic pharmaceutical products manufactured by Wockhardt Limited. Wockhardt USA denies the remaining averments of paragraph 4.

5. Wockhardt USA admits the averments of paragraph 5.

6. Wockhardt USA admits the averments of paragraph 6.

7. Wockhardt USA admits that Orion purports to assert claims under the patent laws of the United States but denies that any of those claims are valid or sustainable. Wockhardt USA admits that this Court has subject matter jurisdiction over this action and that venue is proper because Wockhardt USA and Wockhardt Limited have agreed to venue in this Court for the purposes of this action. Wockhardt USA denies the remaining averments of paragraph 7.

8. Upon information and belief, Wockhardt USA admits that Orion-yhtymä Oy is listed as the owner of United States Patent No. 5,446,194 ("the '194 patent") on the face of the patent, but denies that the '194 patent was "duly and legally" issued. Wockhardt USA admits that a copy of the '194 patent is attached as Exhibit A to the Complaint. Wockhardt USA lacks knowledge or information sufficient to form a belief as to the truth of the remaining averments of paragraph 8 and, therefore, denies the same.

9. Upon information and belief, Wockhardt USA admits that Orion-yhtymä Oy is listed as the owner of United States Patent No. 5,135,950 ("the '950 patent") on the face of the patent, but denies that the '950 patent was "duly and legally" issued. Wockhardt USA admits that a copy of the '950 patent is attached as Exhibit B to the Complaint. Wockhardt USA lacks

knowledge or information sufficient to form a belief as to the truth of the remaining averments of paragraph 9 and, therefore, denies the same.

10. Upon information and belief, Wockhardt USA admits that Orion is the applicant listed in the FDA's *Approved Drug Products with Therapeutic Equivalence Evaluations* (the "Orange Book") as the holder of a New Drug Application ("NDA") for the use of entacapone for the treatment of Parkinson's Disease as an adjunct to levodopa/carbidopa therapy. Wockhardt USA lacks knowledge or information sufficient to form a belief as to the truth of the remaining averments of paragraph 10 and, therefore, denies the same.

11. Upon information and belief, Wockhardt USA admits that Comtan® is the proprietary name of a drug product based on the active ingredient entacapone approved by the FDA for use in the treatment of Parkinson's disease. Wockhardt USA lacks knowledge or information sufficient to form a belief as to the truth of the remaining averments of paragraph 11 and, therefore, denies the same.

12. Wockhardt USA admits that, pursuant to 21 U.S.C. § 355(j), Wockhardt Limited submitted Abbreviated New Drug Application ("ANDA") No. 78-941 to obtain approval to engage in the commercial manufacture, use, importation, offer for sale, and/or sale of entacapone 200 mg tablets ("the Wockhardt Product") for the treatment of Parkinson's disease before the expiration of the '194 or '950 patents. Wockhardt USA admits that Dr. Brij Khera is identified in the ANDA as Wockhardt Limited's authorized U.S. agent for purposes of the ANDA. Wockhardt USA denies the remaining averments of paragraph 12.

13. Wockhardt USA admits that, pursuant to 21 U.S.C. § 355(j)(2)(A)(vii)(IV), Wockhardt Limited included in ANDA No. 78-941 a certification stating that, in the opinion of Wockhardt Limited and to the best of its knowledge, the '194 and '950 patents, as well as United

States Patent No. 6,599,530 ("the '530 patent"), are invalid, unenforceable, or will not be infringed by the commercial manufacture, use, importation, offer for sale, and/or sale the Wockhardt Product.

14. Wockhardt USA admits the averments of paragraph 14.

15. Wockhardt USA admits that the package insert for the Wockhardt Product will comply with the requirements set forth in 21 U.S.C. § 355(j)(2)(A)(v) and 21 C.F.R. § 314.94(a)(8). Wockhardt USA denies the remaining averments of paragraph 15.

COUNT I

16. Wockhardt USA repeats and incorporates by reference its responses to paragraphs 1-15 as if fully set forth herein.

17. Wockhardt USA denies that the commercial manufacture, use, importation, offer for sale, and/or sale of the Wockhardt Product will infringe any valid claim of the '194 patent. Wockhardt USA denies the remaining averments of Paragraph 17.

18. Wockhardt USA denies the averments of paragraph 18.

COUNT II

19. Wockhardt USA repeats and incorporates by reference its responses to paragraphs 1-15 as if fully set forth herein.

20. Wockhardt USA denies the averments of paragraph 20.

21. Wockhardt USA denies the averments of paragraph 21.

22. Wockhardt USA denies the averments of paragraph 22.

COUNT III

23. Wockhardt USA repeats and incorporates by reference its responses to paragraphs 1-22 as if fully set forth herein.

24. Wockhardt USA denies the averments of paragraph 24.

25. Wockhardt USA admits that it intends to sell the Wockhardt Product for use in the treatment of Parkinson's disease after Wockhardt Limited obtains FDA approval for such sales. Wockhardt USA denies the remaining averments of paragraph 25.

26. Wockhardt USA denies that the commercial manufacture, use, importation, offer for sale, and/or sale of the Wockhardt Product, once approved by the FDA, will infringe any valid claim of the '194 patent. Wockhardt USA denies the remaining averments of paragraph 26.

27. Wockhardt USA denies the averments of paragraph 27.

COUNT IV

28. Wockhardt USA repeats and incorporates by reference its responses to paragraphs 1-22 as if fully set forth herein.

29. Wockhardt USA denies the averments of paragraph 29.

30. Wockhardt USA admits that it intends to sell the Wockhardt Product for use in the treatment of Parkinson's disease after Wockhardt Limited obtains FDA approval for such sales. Wockhardt USA denies the remaining averments of paragraph 30.

31. Wockhardt USA denies that the commercial manufacture, use, importation, offer for sale, and/or sale of the Wockhardt Product, once approved by the FDA, will infringe any valid claim of the '950 patent. Wockhardt USA denies the remaining averments of paragraph 31.

32. Wockhardt USA denies the averments of paragraph 32.

COUNT V

33. Wockhardt USA repeats and incorporates by reference its responses to paragraphs 1-32 as if fully set forth herein.

34. Wockhardt USA denies the averments of paragraph 34.

35. Wockhardt USA denies the averments of paragraph 35.

36. Wockhardt USA denies that Orion is entitled to the relief requested in its Prayer for Relief, or to any other relief.

First Affirmative Defense
Noninfringement of the '194 Patent

37. The commercial manufacture, use, importation, offer for sale, and/or sale of the Wockhardt Product will not infringe any valid claim of the '194 patent.

38. Wockhardt USA has not infringed the '194 patent through Wockhardt Limited's filing of ANDA No. 78-941.

Second Affirmative Defense
Noninfringement of the '950 Patent

39. The commercial manufacture, use, importation, offer for sale, and/or sale of the Wockhardt Product will not infringe any valid claim of the '950 patent.

40. Wockhardt USA has not infringed the '950 patent through Wockhardt Limited's filing of ANDA No. 78-941.

Third Affirmative Defense
Invalidity of the '194 Patent

41. Each claim of the '194 patent is invalid for failure to comply with one or more provisions set forth in the patent laws of the United States, 35 U.S.C. § 1 *et seq.*, and/or related judicial doctrine.

Fourth Affirmative Defense
Invalidity of the '950 Patent

42. Each claim of the '950 patent is invalid for failure to comply with one or more provisions set forth in the patent laws of the United States, 35 U.S.C. § 1 *et seq.*

Fifth Affirmative Defense
Failure to State a Claim

43. To the extent the Complaint purports to allege that this case is exceptional under 35 U.S.C. § 285 or otherwise seeks an award of attorneys' fees, the Complaint fails to state a claim upon which relief can be granted.

COUNTERCLAIMS

Wockhardt USA, for its counterclaims against Orion, alleges as follows:

Nature of the Action

1. This is an action for a declaration of patent noninfringement and invalidity arising under the Declaratory Judgment Act, 28 U.S.C. § 2201 *et seq.*, and the patent laws of the United States, 35. U.S.C. § 1 *et seq.*

2. This Court has jurisdiction over the subject matter of this action pursuant to 28 U.S.C. §§ 1331, 1338, and 1367.

3. This Court has jurisdiction over Orion.

4. Venue is proper in this judicial district pursuant to 28 U.S.C. §§ 1391(b), (c), and (d) and 1400(b).

5. Orion has created an actual and justiciable case or controversy between itself and Wockhardt USA.

The Parties

6. Wockhardt Limited is a corporation organized and existing under the laws of India and has a place of business at Wockhardt Towers, Bandra-Kurla Complex Bandra (East) Mumbai - 400 051, Maharashtra, India.

7. Wockhardt USA is a corporation organized and existing under the laws of the State of Delaware and has a place of business at 135 Route 202/206, Bedminster, New Jersey, 07921.

8. Upon information and belief, Orion is a corporation organized and existing under the laws of Finland and has a principal or regular and established place of business at Orionintie 1, FI-02200 Espoo, Finland. Upon information and belief, Orion is engaged in the business of manufacturing, marketing, and distributing pharmaceutical products around the world.

The Patents and Related Drug Product

9. Pursuant to 21 U.S.C. § 355(j), the Federal Food, Drug and Cosmetic Act ("FDCA") authorizes a generic drug company to submit an ANDA to the FDA for approval of a generic drug product that has the same active ingredient as, and is bioequivalent to, a drug product that the FDA has already approved pursuant to an NDA.

10. Pursuant to 21 U.S.C. § 355(b), the FDCA requires NDA holders to disclose to the FDA the patent numbers and expiration dates of any patent that claims the drug or a method of using the drug for which an NDA is submitted. The FDA then lists those patents in the Orange Book.

11. Pursuant to 21 U.S.C. § 355(j)(2)(A)(vii)(IV), if a generic drug company seeks approval to market a generic drug product before the expiration of a patent listed in the Orange Book, the generic drug company must include a certification in its ANDA that the patent is

invalid, unenforceable, or will not be infringed by the generic drug product ("Paragraph IV Certification").

12. Pursuant to 21 U.S.C. § 355(j)(2)(B), if the generic drug company includes a Paragraph IV Certification in its ANDA, the generic drug company must send the NDA holder and the patent owner notice of that certification, including a detailed statement of the factual and legal basis for the generic drug company's opinion that the patent is invalid, unenforceable, or will not be infringed ("Notice Letter").

13. Pursuant to 21 U.S.C. § 355(j)(5)(B)(iii), if a suit for patent infringement is brought within 45 days of receiving the Notice Letter, the FDA will not approve the generic drug company's ANDA for 30 months or until resolution of the patent infringement action.

14. Upon information and belief, Orion is the holder of NDA No. 20-796 for oral entacapone (200 mg tablets). Upon information and belief, the trade name of Orion entacapone is Comtan.

15. Upon information and belief, Orion is the owner of United States Patent No. 5,446,194 ("the '194 patent"), United States Patent No. 6,599,530 ("the '530 patent"), and United States Patent No. 5,135,950 ("the '950 patent"). Copies of the '194 and '950 patents are attached as Exhibits A and B to Orion's Complaint. A copy of the '530 patent is attached hereto as Exhibit A.

16. Upon information and belief, Orion caused the '194, '530, and '950 patents to be listed in the Orange Book entry for Comtan, NDA 20-796.

17. Wockhardt Limited submitted ANDA No. 78-941 to the FDA to obtain approval to engage in the commercial manufacture, use, importation, offer for sale, and/or sale of the Wockhardt Product before the expiration of the '194, '530, and '950 patents. Wockhardt

Limited included in ANDA No. 78-941 a Paragraph IV Certification stating that, in the opinion of Wockhardt Limited, and to the best of its knowledge, the '194, '530, and '950 patents are invalid, unenforceable, or will not be infringed by the commercial manufacture, use, importation, offer for sale, and/or sale of the Wockhardt Product.

18. On August 3, 2007, counsel for Wockhardt Limited and Wockhardt USA sent Orion a Notice Letter that included a detailed statement of the factual and legal basis for Wockhardt Limited's opinion. Pursuant to 21 U.S.C. § 355(j)(5)(C), the Notice Letter was accompanied by an Offer of Confidential Access to ANDA No. 78-941.

19. On or about September 13, 2007, Orion filed a Complaint in this action against Wockhardt USA and Wockhardt Limited alleging infringement of the '194 and '950 patents. Orion asserted in its Complaint, and continues to assert, that the submission of Wockhardt Limited's ANDA No. 78-941 was an act of infringement of the '194 and '950 patents under 35 U.S.C. § 271(e)(2). Orion also asserted in its Complaint, and continues to assert, that the commercial manufacture, use, importation, offer for sale, and/or sale of the Wockhardt Product will infringe one or more claims of the '194 and '950 patents under 35 U.S.C. § 271.

20. Orion has publicly stated that it will vigorously defend its intellectual property rights related to Comtan.

21. In a Stock Exchange Release dated September 13, 2007, Orion publicly announced its filing of the instant lawsuit and stated that it "will vigorously defend the intellectual property rights covering Comtan."

22. Orion's publicly accessible website, available at www.orion.fi, states that "in developing its products, Orion endeavours to protect them efficiently and over a wide area, whilst defending the rights of its products diligently."

23. Orion has not yet sued Wockhardt USA for infringement of the '530 patent, even though that patent continues to be listed in the Orange Book entry for Comtan, NDA 20-796, and even though Orion has made public statements that it intends to vigorously assert its intellectual property rights related to Comtan. This creates uncertainty for Wockhardt USA as to its legal rights and the possibility of future litigation concerning the '530 patent.

24. Orion's assertion against Wockhardt USA of claims of infringement of the '194 and '950 patents after being advised by Wockhardt Limited that there is no basis for those claims, as well as other conduct yet to be discovered, renders this case exceptional within the meaning of 35 U.S.C. § 285.

25. Wockhardt USA has no adequate remedy at law. The actions and assertions made by Orion with respect to the '194, '530, and '950 patents have caused and will continue to cause irreparable injury to the rights of Wockhardt USA.

Counterclaim Count I
Declaratory Judgment of Noninfringement of the '194 Patent

26. Wockhardt USA repeats and realleges the averments contained in paragraphs 1-25 of its counterclaims.

27. Wockhardt USA seeks a declaratory judgment of noninfringement of each claim of the '194 patent.

28. An actual and justiciable case or controversy exists between Orion and Wockhardt USA concerning the alleged infringement of the '194 patent.

29. The commercial manufacture, use, importation, offer for sale, and/or sale of the Wockhardt Product will not infringe any valid claim of the '194 patent.

30. Wockhardt USA has not infringed the '194 patent through Wockhardt Limited's filing of ANDA No. 78-941 because the commercial manufacture, use, importation, offer for sale, and/or sale of the Wockhardt Product will not infringe any valid claim of the '194 patent.

Counterclaim Count II
Declaratory Judgment of Invalidity of the '194 Patent

31. Wockhardt USA repeats and realleges the averments contained in paragraphs 1-25 of its counterclaims.

32. Wockhardt USA seeks a declaratory judgment of invalidity of each claim of the '194 patent and therefore that Wockhardt USA's commercial manufacture, use, importation, offer for sale, and/or sale of the Wockhardt Product in the United States will not infringe any valid claim of the '194 patent.

33. An actual and justiciable case or controversy exists between Orion and Wockhardt USA concerning the invalidity of the '194 patent.

34. Each claim of the '194 patent is invalid for failure to comply with one or more provisions set forth in the patent laws of the United States, 35 U.S.C. § 1 *et seq.*, and/or related judicial doctrine.

Counterclaim Count III
Declaratory Judgment of Noninfringement of the '950 Patent

35. Wockhardt USA repeats and realleges the averments contained in paragraphs 1-25 of its counterclaims.

36. Wockhardt USA seeks a declaratory judgment of noninfringement of each claim of the '950 patent.

37. An actual and justiciable case or controversy exists between Orion and Wockhardt USA concerning the alleged infringement of the '950 patent.

38. The commercial manufacture, use, importation, offer for sale, and/or sale of the Wockhardt Product will not infringe any valid claim of the '950 patent.

39. Wockhardt USA has not infringed the '950 patent through Wockhardt Limited's filing of ANDA No. 78-941 because the commercial manufacture, use, importation, offer for sale, and/or sale of the Wockhardt Product will not infringe any valid claim of the '950 patent.

Counterclaim Count IV
Declaratory Judgment of Invalidity of the '950 Patent

40. Wockhardt USA repeats and realleges the averments contained in paragraphs 1-25 of its counterclaims.

41. Wockhardt USA seeks a declaratory judgment of invalidity of each claim of the '950 patent and therefore that Wockhardt USA's commercial manufacture, use, importation, offer for sale, sale, or importation of the Wockhardt Product will not infringe any valid claim of the '950 patent.

42. An actual and justiciable case or controversy exists between Orion and Wockhardt USA concerning the invalidity of the '950 patent.

43. Each claim of the '950 patent is invalid for failure to comply with one or more provisions set forth in the patent laws of the United States, 35 U.S.C. § 1 *et seq*.

Counterclaim Count V
Declaratory Judgment of Noninfringement of the '530 Patent

44. Wockhardt USA repeats and realleges the averments contained in paragraphs 1-25 of its counterclaims.

45. Wockhardt USA seeks a declaratory judgment of noninfringement of each claim of the '530 patent.

46. Based on, *inter alia*, Wockhardt Limited's submission of ANDA No. 78-941 with a Paragraph IV Certification regarding the '530 patent and Orion's bringing suit on some, but not

all, of the patents listed in the Paragraph IV Certification, an actual and justiciable case or controversy exists between Wockhardt USA and Orion concerning the noninfringement of the '530 patent.

47. The commercial manufacture, use, importation, offer for sale, and/or sale of the Wockhardt Product will not infringe any valid claim of the '530 patent.

48. Wockhardt USA has not infringed the '530 patent through Wockhardt Limited's filing of ANDA No. 78-941 because the commercial manufacture, use, importation, offer for sale, and/or sale of the Wockhardt Product will not infringe any valid claim of the '530 patent.

Counterclaim Count VI
Declaratory Judgment of Invalidity of the '530 Patent

49. Wockhardt USA repeats and realleges the averments contained in paragraphs 1-25 of its counterclaims.

50. Wockhardt Limited seeks a declaratory judgment of invalidity of each claim of the '530 patent and, therefore, that Wockhardt USA's commercial manufacture, use, importation, offer for sale, and/or sale of the Wockhardt Product in the United States will not infringe any valid claim of the '530 patent.

51. Based on, *inter alia*, Wockhardt Limited's submission of ANDA No. 78-941 with a Paragraph IV Certification regarding the '530 patent and Orion's bringing suit on some, but not all, of the patents listed in the Paragraph IV Certification, an actual and justiciable case or controversy exists between Wockhardt USA and Orion concerning the invalidity of the '530 patent.

52. Each claim of the '530 patent is invalid for failure to comply with one or more provisions set forth in the patent laws of the United States, 35 U.S.C. § 1 *et seq*.

PRAYER FOR RELIEF

WHEREFORE, Wockhardt USA respectfully requests the Court enter judgment in its favor:

(a) Dismissing each claim of the Complaint with prejudice;

(b) Declaring that the commercial manufacture, use, importation, offer for sale, and/or sale of the Wockhardt Product will not infringe, contribute to the infringement of, or induce the infringement of any valid claim of the '194, '530, and '950 patents;

(c) Declaring that the claims of the '194, '530, and '950 patents are invalid;

(d) Permanently enjoining Orion, its officers, agents, directors, servants, employees, subsidiaries and assigns, and all those acting under the authority of or in privity with them or with any of them, from asserting or otherwise seeking to enforce the '194, '530, and '950 patents against Wockhardt USA;

(e) Adjudging this to be an exceptional case under 35 U.S.C. § 285 and awarding Wockhardt USA its costs and attorneys' fees incurred in this action; and

(f) Granting Wockhardt USA such other and further relief as this Court may deem just and proper.

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Dated: November 21, 2007
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EXHIBIT A

US006599530B2

(12) **United States Patent**
Vahervuo

(10) **Patent No.: US 6,599,530 B2**
(45) **Date of Patent: Jul. 29, 2003**

(54) **ORAL COMPACTED COMPOSITION COMPRISING CATECHOL DERIVATIVES**

(75) Inventor: **Kari Vahervuo**, Espoo (FI)

(73) Assignee: **Orion Corporation**, Espoo (FI)

(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.

(21) Appl. No.: **09/152,263**

(22) Filed: **Sep. 14, 1998**

(65) **Prior Publication Data**

US 2002/0132009 A1 Sep. 19, 2002

(51) **Int. Cl.**[7] **A61K 9/20**
(52) **U.S. Cl.** **424/464**; 424/465; 424/488; 514/676; 514/678; 514/689; 514/772; 514/781
(58) **Field of Search** 424/464, 465, 424/488; 514/676, 678, 689, 772, 781

(56) **References Cited**

U.S. PATENT DOCUMENTS

5,380,535 A * 1/1995 Geyer et al. 424/484
5,446,194 A * 8/1995 Backstrom et al. 558/401
5,489,614 A * 2/1996 Korkolainen et al. 514/676

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A. Wade and P. J. Weller, Croscarmellose Sodium, *Handbook of Pharmaceutical Excipients*, Second Edition, The Pharmaceutical Press, London, 1994, 141–142.

Co–pending U.S. application No. 09/787,027, filed on Jun. 25, 2001.

Fielder, "Lexikon Der Hilfsstoffe" Editio Canteor Verlag, Aulendorf, Germany XP 002126381, 1996.

Co–pending U.S. application No. 09/605,529, filed on Jun. 29, 2000.

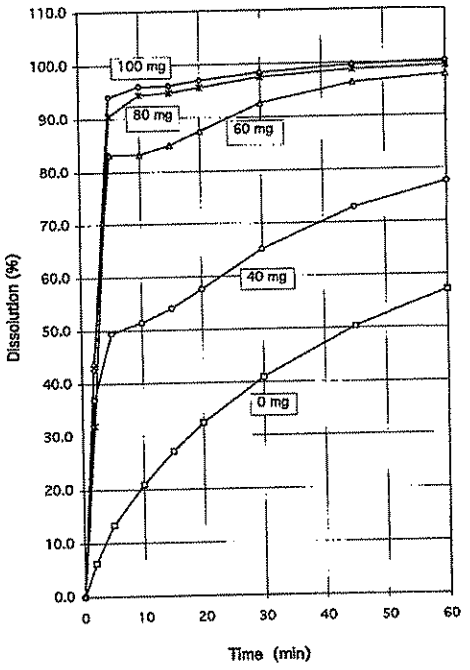
* cited by examiner

Primary Examiner—Thurman K. Page
Assistant Examiner—Lakshimi Channavajjala
(74) *Attorney, Agent, or Firm*—Finnegan, Henderson, Farabow, Garrett & Dunner, LLP

(57) **ABSTRACT**

The present invention relates to an oral compacted composition comprising entacapone, nitecapone, or a pharmaceutically acceptable salt thereof and croscarmellose sodium. The composition is premised on the discovery that croscarmellose sodium increases the release rate of entacapone or nitecapone from an oral compacted composition. Preferably the amount of croscarmellose sodium in the composition is at least 6% by weight, preferably from about 8% to about 16% by weight, especially from about 10% to about 14% by weight.

20 Claims, 2 Drawing Sheets



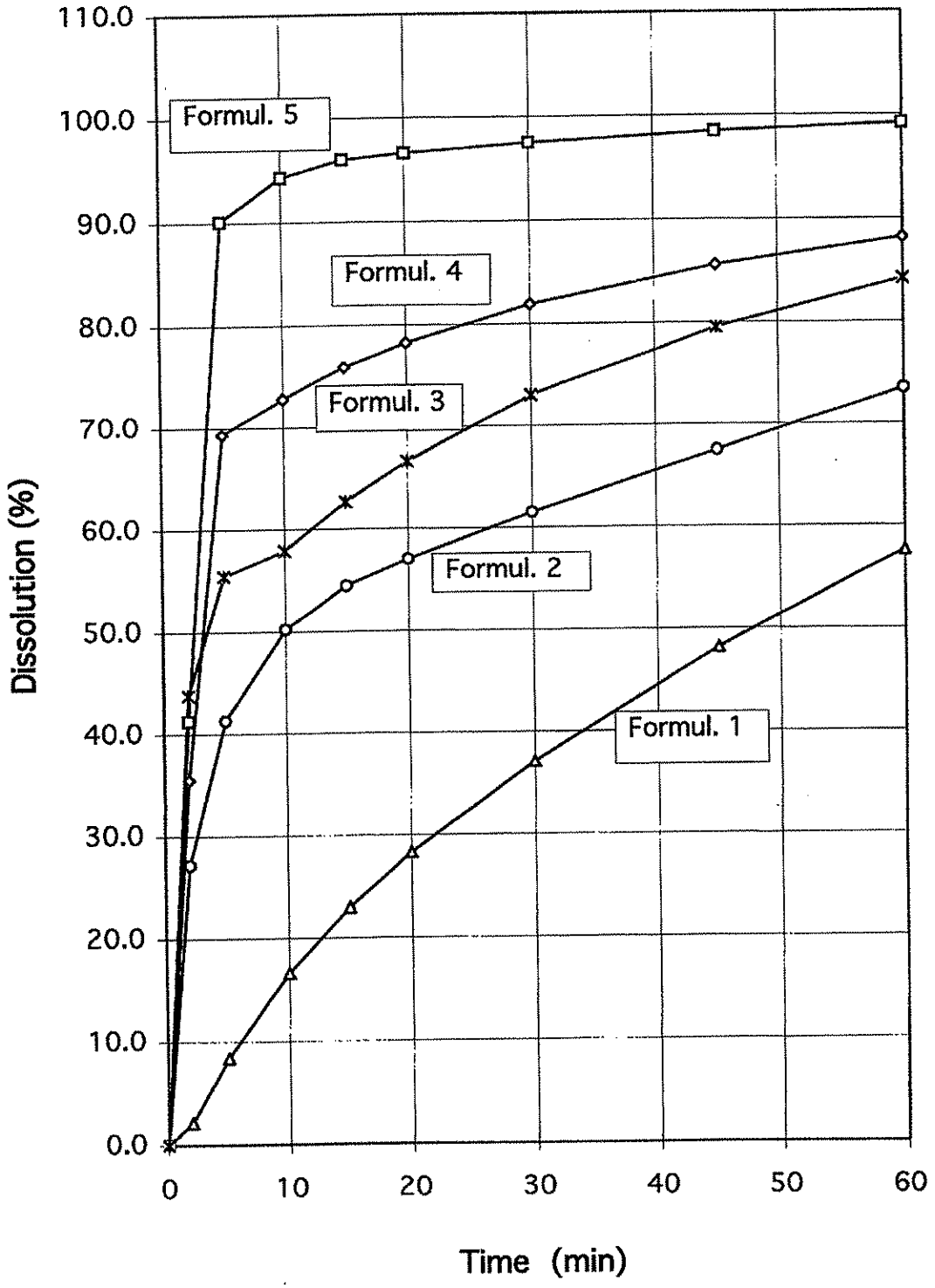

110.0
100.0
90.0
80.0
70.0
60.0
50.0
40.0
30.0
20.0
10.0
0.0
Dissolution (%)
0
10
20
30
40
50
60
Time (min)
Formul. 5
Formul. 4
Formul. 3
Formul. 2
Formul. 1

Fig. 1

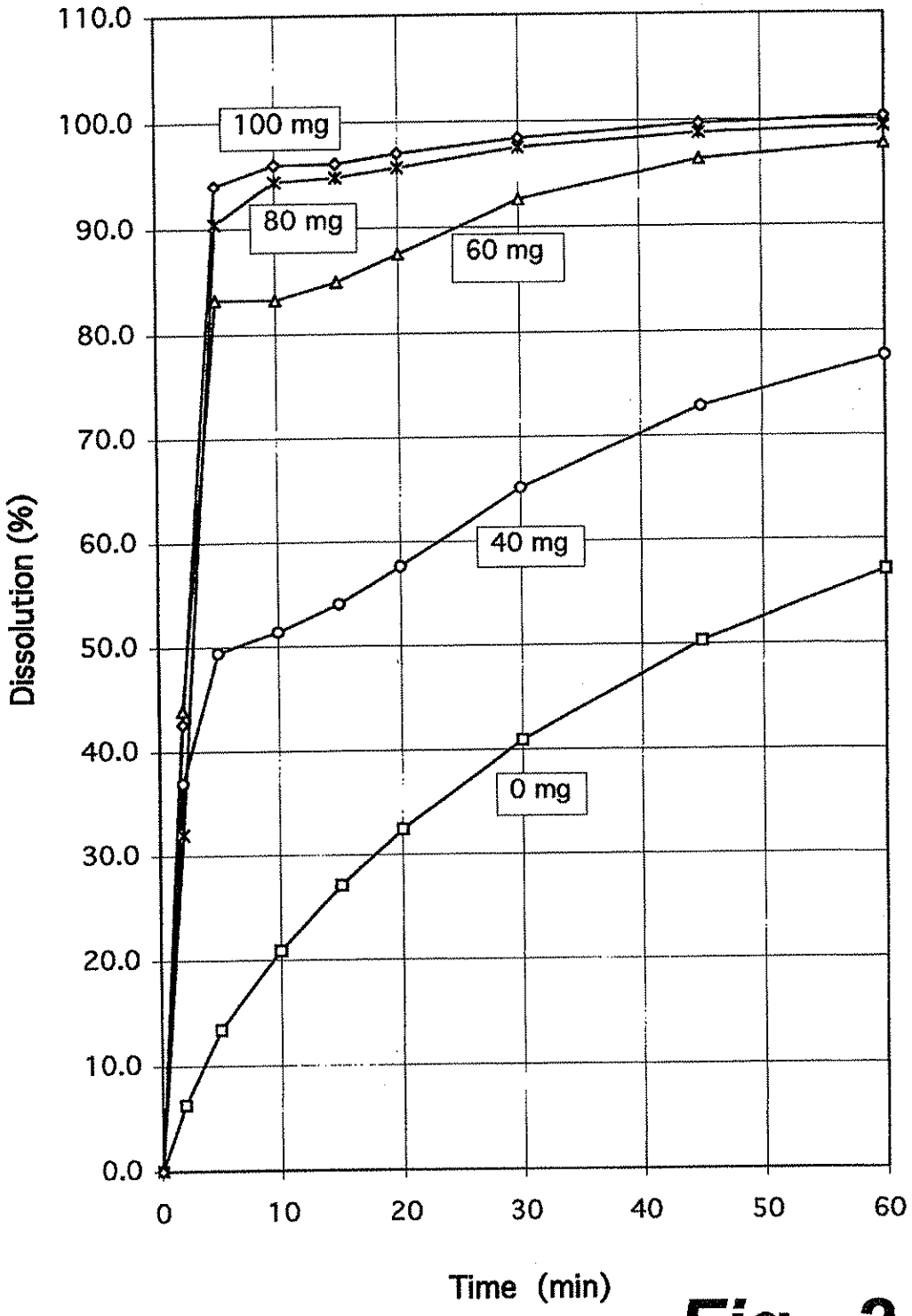

110.0
100.0
90.0
80.0
70.0
60.0
50.0
40.0
30.0
20.0
10.0
0.0
Dissolution (%)
100 mg
80 mg
60 mg
40 mg
0 mg
0
10
20
30
40
50
60
Time (min)

Fig. 2

ORAL COMPACTED COMPOSITION COMPRISING CATECHOL DERIVATIVES

BACKGROUND OF THE INVENTION

The present invention relates to a new pharmaceutical composition comprising a catechol derivative and croscarmellose sodium as a dissolution enhancing agent. Accordingly, the present invention relates to an oral compacted composition comprising entacapone, nitecapone, or a pharmaceutically acceptable salt thereof, and croscarmellose sodium (Ac—Di—Sol) as a dissolution enhancing agent. Particularly, the invention relates to an oral compacted composition comprising entacapone, nitecapone, or a pharmaceutically acceptable salt thereof and croscarmellose sodium, wherein the amount of croscarmellose sodium in the composition is at least 6% by weight, more preferably from about 8% to about 16% by weight, especially from about 10% to 14% by weight. Preferably the oral compacted composition is in the form of a tablet. Further, the present invention relates to a method of preparing an oral compacted composition comprising entacapone, nitecapone, or pharmaceutically acceptable salt thereof, and croscarmellose sodium. The present invention also relates to the use of croscarmellose sodium in the manufacture of an oral compacted composition comprising entacapone, nitecapone, or a pharmaceutically acceptable salt thereof.

The chemical names of entacapone and nitecapone are (E)-2-cyano-3-(3,4-dihydroxy-5-nitrophenyl)-N,N-diethyl-2-propenamide and 3-(3,4-dihydroxy-5-nitrobenzylidene)-2,4-pentanedione, respectively. Entacapone and nitecapone are described in U.S. Pat. No. 5,446,194 as catechol-O-methyltransferase (COMT) inhibitors. Enteral and parenteral routes of administration are discussed in U.S. Pat. No. 5,446,194.

It is desirable that entacapone, nitecapone, or a pharmaceutically acceptable salt thereof, is released from the oral composition as soon as possible after ingesting it. This can normally be achieved by using a dissolution enhancing agent in the pharmaceutical composition. The dissolution enhancing agent may be a disintegrant or any other agent that enhances the dissolution. There is a vast selection of different dissolution enhancing agents, including disintegrants, on the market, which have different chemical and physical characteristics. When selecting the best dissolution enhancing agent to be used in a pharmaceutical composition in combination with an active agent, numerous factors have to be considered, e.g., the chemical and physical characteristics of the active agent and the dissolution enhancing agent, the chemical and physical characteristics of the auxiliary agents, such as diluents and binders, the method of preparing the composition, etc.

Croscarmellose sodium is a cross-linked polymer of carboxymethyl-cellulose sodium. According to the Handbook of Pharmaceutical Excipients (Ainley Wade and Paul J. Weller, Second Edition, The Pharmaceutical Press, London, 1994), it is used in oral pharmaceutical formulations as a disintegrant for tablets, capsules, and granules. Typically, concentrations from 0.5 to 5% w/w are used as a tablet disintegrant.

Neither the above-cited patent nor any other patent or publication of which applicants are aware describes an oral compacted composition comprising entacapone, nitecapone, or pharmaceutically acceptable salt thereof, and croscarmellose sodium.

SUMMARY OF THE INVENTION

Applicants have discovered that croscarmellose sodium is a superior disintegrant to be used in an oral compacted composition comprising entacapone, nitecapone, or pharmaceutically acceptable salt thereof. Accordingly, an object of the invention is to provide an oral compacted composition comprising entacapone, nitecapone, or a pharmaceutically acceptable salt thereof and croscarmellose sodium. The composition is premised on the discovery that croscarmellose sodium essentially increases the release rate of entacapone or nitecapone from an oral compacted composition. Particularly, an object of the invention is to provide an oral compacted composition comprising entacapone, nitecapone, or a pharmaceutically acceptable salt thereof and croscarmellose sodium, wherein the amount of croscarmellose sodium in the composition is at least 6% by weight, more preferably from about 8% to about 16% by weight, especially from about 10% to 14% by weight.

Preferably, the oral compacted composition is in the form of a tablet and, therefore, an object of the invention is to provide a tablet comprising entacapone, nitecapone, or a pharmaceutically acceptable salt thereof and croscarmellose sodium.

A further object of the invention is to provide a tablet comprising entacapone, nitecapone, or a pharmaceutically acceptable salt thereof and croscarmellose sodium, wherein the amount of croscarmellose sodium is at least 6% by weight, more preferably from about 8% to about 16% by weight, especially from about 10% to about 14% by weight.

An object of the invention is also to provide a method for preparing an oral compacted composition comprising entacapone, nitecapone, or a pharmaceutically acceptable salt thereof, and croscarmellose sodium, wherein said method comprises mixing a pharmaceutically effective amount of entacapone, nitecapone, or a pharmaceutically acceptable salt thereof, one or more auxiliary agents, and croscarmellose sodium to obtain a first mixture; compacting and crushing the first mixture one or more times to obtain a plurality of granules; adding a lubricant, a glidant or a mixture thereof to the granules to obtain a second mixture; and compressing the second mixture into a plurality of tablets.

An object of the invention is to provide a method of inhibiting catechol-O-methyltransferase by administering to a patient in need thereof an oral compacted composition comprising entacapone, nitecapone, or a pharmaceutically acceptable salt thereof.

A further aspect of the invention relates to the use of croscarmellose sodium in the manufacture of an oral compacted composition comprising entacapone, nitecapone, or a pharmaceutically acceptable salt thereof.

Additional objects and advantages of the invention will be set forth in part in the description which follows, and in part will be obvious from the description, or may be learned by practice of the invention. The objects and advantages of the invention will be realized and attained by means of the elements and combinations particularly pointed out in the appended claims.

It is to be understood that both the foregoing general description and the following detailed description are exemplary and explanatory only and are not restrictive of the invention, as claimed.

BRIEF DESCRIPTION OF THE DRAWINGS

FIG. 1 shows the effect of different dissolution enhancing agents on the dissolution of compacted entacapone 200 mg tablet formulations.

FIG. 2 shows the effect of croscarmellose sodium on the dissolution of compacted entacapone 200 mg tablet formulations.

DETAILED DESCRIPTION OF THE INVENTION

Applicants have surprisingly discovered that croscarmellose sodium is effective for increasing the disintegration rate of an oral compacted composition comprising entacapone, nitecapone or a pharmaceutically acceptable salt thereof.

An oral compacted composition is a composition wherein a mixture of an active agent, one or more auxiliary agents and a dissolution enhancing agent is first compacted, then crushed into granules, and further the granules are tabletted or enclosed in a capsule. The best dissolution enhancing agent is the one that releases the active agent from the composition as fast as possible.

Applicants found that croscarmellose sodium is unexpectedly more efficient in releasing entacapone, nitecapone or a pharmaceutically acceptable salt thereof from an oral compacted composition than other common dissolution improving agents, such as starch, pregelatinized starch, microcrystalline cellulose, mannitol, sodium starch glycolate, or sodium lauryl sulphate. The dissolution test of Example 1 shows that 90.1% of entacapone is dissolved from a tablet comprising croscarmellose sodium as a disintegrant in 5 minutes (see FIG. 1). This result is far superior when compared to 69.3%, 55.4%, 41.3%, and 8.4% for sodium lauryl sulphate, sodium starch glycolate, pregelatinized starch, and mannitol containing tablets, respectively.

Croscarmellose sodium is in the oral compacted composition in an amount to enhance the dissolution of the active agent. Applicants have surprisingly discovered that the best dissolution results for the oral compacted compositions of the invention are achieved when the amount of croscarmellose sodium is far more than what is suggested in the art. Accordingly, it has been found that the amount of croscarmellose sodium in the oral compacted composition is preferably at least 6% by weight. More preferably, the amount of croscarmellose sodium is from about 8% to about 16% by weight, especially from about 10% to 14% by weight.

The amount of entacapone, nitecapone or a pharmaceutically acceptable salt thereof in the oral compacted composition is dependent on numerous factors known to one skilled in the art, such as, the type of mammal, the condition to be treated, the desired duration of use, etc. The compacted composition of the invention may also contain one or more other pharmaceutically active agents. The amount of entacapone in a tablet according to the invention can be about 5–400 mg, preferably about 100–200 mg, more preferably 200 mg.

Entacapone and nitecapone can be prepared, for example, as described in U.S. Pat. No. 5,446,194.

An oral compacted composition according to the invention can be prepared by mixing a pharmaceutically effective amount of entacapone, nitecapone, or a pharmaceutically acceptable salt thereof, one or more auxiliary agents and croscarmellose sodium and further compacting and crushing the mixture to form granules. The compacting and crushing can be proceeded one or more times. The granules are then mixed with a lubricant, a glidant or a mixture thereof and the mixture is compressed into tablets. The tablets may be coated after tabletting. The granules may also be encapsulated to form capsules. The auxiliary agent may be a diluent, a binder or a mixture of different diluents and/or binders. Preferably at least one of the auxiliary agents is water soluble. Suitable diluents and binders include, e.g., microcrystalline cellulose, hypromellose (HPMC), povidone, starch, lactose, sucrose, mannitol, sorbitol, etc. Suitable lubricants and glidants include, e.g., magnesium stearate, calcium stearate, hydrogenated vegetable oil, talc, colloidal silicon dioxide, etc.

One skilled in the art would recognize other suitable auxiliary agents, lubricants and glidants that can be used in the composition of the present invention.

The invention will be further clarified by the following examples, which are intended to be purely exemplary of the invention.

EXAMPLE 1

The dissolution of entacapone 200 mg tablet formulations containing different disintegrants were tested. The tablets were prepared by mixing, compacting, crushing and compressing as described above. The formulations were as described in Table 1. The dissolution of each formulation was tested using the basket method with a 100 rpm speed and 900 ml medium of phosphate buffer pH 5.8.

The amount of entacapone released was determined by a spectrophotometric method using a UVNIS spectrophotometer. The detection wavelength was 313 nm. The results, which are presented in FIG. 1, show that the formulation containg croscarmellose sodium (Formul. 5) releases entacapone fastest.

TABLE 1

Entacapone 200 mg tablet formulations containing different dissolution enhancing agents used in the dissolution test.

Compound	Formul. 1 (mg)	Formul. 2 (mg)	Formul. 3 (mg)	Formul. 4 (mg)	Formul. 5 (mg)
Entacapone	200	200	200	200	200
Microcryst. cellulose	50	210	410	420	370
Mannitol	400	0	0	0	0
Pregelatinized Starch	0	180	0	0	0
Sodium Starch Glycolate	0	0	40	0	0
Sodium Lauryl Sulphate	0	0	0	30	0
Croscarmellose Sodium	0	0	0	0	80
Magnesium Stearate	10	10	10	10	10

EXAMPLE 2

The effect of croscarmellose sodium on the dissolution of compacted entacapone 200 tablet formulations was tested according to the method described in Example 1. The different formulations, i.e., Formul. 6-Formul. 10, are described in Table 2. The results of the dissolution test are shown in FIG. 2. The formulation containing the most croscarmellose sodium (100 mg) released entacapone the fastest.

TABLE 2

Compacted entacapone 200 mg tablet formulations containing different amounts of croscarmellose sodium.

Compound	Formul. 6 (mg)	Formul. 7 (mg)	Formul. 8 (mg)	Formul. 9 (mg)	Formul. 10 (mg)
Entacapone	200	200	200	200	200
Microcryst. cellulose	445	405	220	200	180
Mannitol	0	0	170	170	170

TABLE 2-continued

Compacted entacapone 200 mg tablet formulations containing different amounts of croscarmellose sodium.

Compound	Formul. 6 (mg)	Formul. 7 (mg)	Formul. 8 (mg)	Formul. 9 (mg)	Formul. 10 (mg)
Croscarmellose Sodium	0	40	60	80	100
Magnesium Stearate	15	15	12	12	12

EXAMPLE 3

Oral compact compositions according to the invention comprising entacapone as an active agent can include for instance those described in Table 3.

TABLE 3

Different oral compacted entacapone 200 mg tablet formulations.

Compound	Formul. 11 (mg)	Formul. 12 (mg)	Formul. 13 (mg)	Formul. 14 (mg)	Formul. 15 (mg)
Entacapone	200	200	200	200	200
Microcrystalline cellulose	290	230	160	190	120
Sucrose	10	0	100	60	190
Mannitol	90	160	80	140	50
Hypromellose (HPMC)	5	0	20	0	10
Croscarmellose Sodium	73	80	82	82	88
Hydrogenated vegetable oil	0	5	38	2	14
Magnesium Stearate	15	8	3	9	11

Those skilled in the art will recognize that while specific embodiments have been illustrated and described, various modifications and changes may be made without departing from the spirit and scope of the invention.

Other embodiments of the invention will be apparent to those skilled in the art from consideration of the specification and practice of the invention disclosed herein. It is intended that the specification and examples be considered as exemplary only, with a true scope and spirit of the invention being indicated by the following claims.

The references discussed herein are specifically incorporated by reference in their entirety.

What is claimed is:

1. An oral compacted composition in the form of a tablet, which comprises a pharmaceutically effective amount of entacapone, nitecapone, or pharmaceutically acceptable salt of entacapone or nitecapone, and croscarmellose sodium in an amount of at least 6% by weight of the composition.

2. An oral compacted composition according to claim **1**, which comprises entacapone or a pharmaceutically acceptable salt thereof.

3. An oral compacted composition according to claim **1**, which comprises nitecapone or a pharmaceutically acceptable salt thereof.

4. An oral compacted composition according to claim **1**, which comprises croscarmellose sodium in an amount of from about 8% to about 16% by weight of the composition.

5. An oral compacted composition according to claim **4**, which comprises croscarmellose sodium in an amount of from about 10% to about 14% by weight of the composition.

6. An oral compacted composition according to claim **1**, which comprises entacapone and about 6% by weight of croscarmellose sodium, and wherein the in vitro dissolution of entacapone is at least about 65% a over a period of about 30 minutes when measured using the basket method at 100 rpm speed and 900 ml medium of phosphate buffer at pH 58.

7. An oral compacted composition according to claim **1**, which comprises entacapone and about 9% by weight of croscarmellose sodium, and wherein the in vitro dissolution of entacapone is at least about 92% over a period of about 30 minutes when measured using the basket method at 100 rpm speed and 900 ml medium of phosphate buffer at pH 5.8.

8. An oral compacted composition according to claim **2**, which comprises from about 5 mg to about 400 mg of entacapone or pharmaceutically acceptable salt thereof.

9. An oral compacted composition according to claim **8**, which comprises from about 100 mg to about 200 mg of entacapone or pharmaceutically acceptable salt thereof.

10. An oral compacted composition according to claim **9**, which comprises about 200 mg of entacapone or pharmaceutically acceptable salt thereof.

11. An oral compacted composition in the form of a tablet, which comprises from about 100 mg or 200 mg of entacapone or pharmaceutically acceptable salt thereof, and croscarmellose sodium in an amount of at least 6% by weight of the composition.

12. A method for preparing an oral compacted composition in the form of a tablet wherein the composition comprises entacapone, nitecapone, or a pharmaceutically acceptable salt of entacapone or nitecapone, and the croscarmellose sodium in an amount of at least 6% by weight of the composition, which comprises:

a) mixing a pharmaceutically effective amount of entacapone, nitecapone, or pharmaceutically acceptable salt of entacapone or nitecapone, one or more auxiliary agents and croscarmellose sodium to obtain a first mixture;

b) compacting and crushing the first mixture one or more times to obtain a plurality of granules;

c) adding a lubricant, a glidant, or a mixture thereof to the granules to obtain a second mixture; and

d) compressing the second mixture into a tablet.

13. A method according to claim **12**, wherein the composition comprises croscarmellose sodium in an amount of from about 8% to about 16% by weight of the composition.

14. A method according to claim **13**, wherein the composition comprises croscarmellose sodium in an amount of from about 10% to about 14% by weight of the composition.

15. A method according claim **12**, wherein at least one of the auxiliary agents is water soluble.

16. A method according to claim 12, wherein the composition comprises from about 5 mg to about 400 mg of entacapone or pharmaceutically acceptable salt thereof.

17. A method according to claim 11, wherein the composition comprises from about 100 mg to about 200 mg of entacapone or pharmaceutically acceptable salt thereof.

18. A method according to the composition comprises about 200 mg of entacapone or pharmaceutically acceptable salt thereof.

19. A method of inhibiting catechol-O-methyltransferase, which comprises administering to a patient in need thereof an oral compacted composition according to claim 1.

20. A method according to claim 19, wherein the oral compacted composition comprises entacapone or a pharmaceutically acceptable salt thereof.

* * * * *

UNITED STATES PATENT AND TRADEMARK OFFICE

CERTIFICATE OF CORRECTION

PATENT NO. : 6,599,530 B2
DATED : July 29, 2003
INVENTOR(S) : Kari Vahervuo

It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

Column 5,
Line 67, "65% a over" should read -- 65% over --.

Column 6,
Line 2, "pH 58." should read -- pH 5.8. --.
Line 35, "100 mg or 200 mg" should read -- 100 mg to 200 mg --.
Line 40, "tablet wherein" should read -- tablet, wherein --.
Line 6, "according claim" should read -- according to claim --.

Column 7,
Line 4, "claim 11," should read -- claim 16, --.
Line 7, "to the" should read -- to claim 17, wherein the --.

Signed and Sealed this

Eleventh Day of November, 2003

JAMES E. ROGAN
Director of the United States Patent and Trademark Office

IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

CERTIFICATE OF SERVICE

I, Philip A. Rovner, hereby certify that on November 21, 2007, the within document was filed with the Clerk of the Court using CM/ECF which will send notification of such filing(s) to the following; that the document was served on the following counsel as indicated; and that the document is available for viewing and downloading from CM/ECF.

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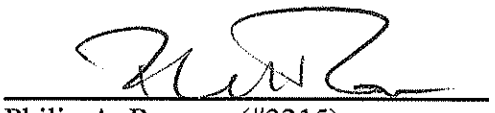

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